## REMARKS

This responds to the Office Action mailed on March 4, 2005, and the documents cited therewith.

Claims 7 and 18 are amended, claim 17 is canceled, and claims 21-23 are added; as a result, claims 1-16 and 18-23 are now pending in this application.

Present claim 7 now depends upon claims 1, 2, or 3. Present claim 18 now incorporates language suggested by the Examiner. New claim 23 is drawn to a method of treating HIV or AIDS. Support for this claim appears in original claim 17. Claims 21 and 22 were added as a result of the change to claim 7. Support for these claims appears in original claims 7 and 8. No new matter has been added.

### *Objection to Claims*

Claims 7 and 8 were objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim may not depend from another multiple dependent claim.

Applicants have removed the dependency upon claim 4 from claim 7. In addition Applicants have added new claims 21 and 22, which are dependent upon claim 4. Support for the new claims appears in original claims 7 and 8. No new matter has been added. Withdrawal of this objection is respectfully requested.

### *Rejection Under 35 U.S.C. § 101*

Claim 17 was rejected under 35 U.S.C. § 101 for allegedly being an improper process by virtue of recitation of the phrase *use of*. Applicants have cancelled claim 17 and added new claim 22, drawn to a method of treating HIV or AIDS. Withdrawal of this rejection is respectfully requested.

### *Rejections Under 35 U.S.C. § 112, 2nd Paragraph*

**Rejection of Claim 11**

Claim 11 was rejected under 35 U.S.C. § 112, 2nd paragraph as being indefinite with respect to the phrase $R^2$ *is the remainder of organic group R*. The Examiner alleged that the claim includes all known organic groups. Office Action at page 2. This rejection is respectfully

traversed.

Claim 11 depends upon claims 1, 2, or 3, and claims 2 and 3 depend directly or indirectly upon claim 1. Claim 1 defines R as an organic substituent that does not interfere with the condensation of **(2)** and **(3)**. One can see by inspection that groups R and X are involved in the cyclization of compound **(1)** to form compound **(6)**, as claimed in method claim 11. The structure of R is not critical so long as it does not interfere with the condensation. The group R is also defined in claim 11 as $-CH_2CH_2CH=C(CH_3)R^2$, which, by virtue of dependence upon claim 1, does not interfere with the condensation of **(2)** and **(3)**. The $R^2$ moiety in formula **(6)** of claim 11 is the residue of this R group after the cyclization reaction. Therefore, the Examiner is incorrect that claim 11 includes all known organic groups.

Withdrawal of this rejection is respectfully requested.

**Rejection of claim 18**

Claim 18 was rejected under 35 U.S.C. § 112, 2nd paragraph as being indefinite with respect to an alleged conflict between the phrases *pharmaceutical composition* and *effective amount.*

Applicants have adopted the Examiner's suggestion; present claim 18 now recites a therapeutically effective amount. Withdrawal of this rejection is respectfully requested.

**Rejection of claim 1**

Claim 1 was rejected under 35 U.S.C. § 112, 2nd paragraph as being indefinite for not positively reciting definitions of R, X, Y, and Z. This rejection is respectfully traversed.

The Examiner is reminded that the current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative recitation. MPEP § 2173.05(i). So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. § 112, 2nd paragraph. *Ibid.* Furthermore, the MPEP states that some latitude in the manner of expression and the aptness of terms should be permitted, and that Examiners should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement. MPEP § 2173.02. Where a group defined generically is not critical and the disclosure gives reasonable assurance

that all compounds embraced by the claim would be useful for the disclosed purpose, the term is not objectionable as "too broad and indefinite." *In re Riat*, 327 F.2d 685, 140 USPQ 471 (CCPA 1964).

Applicants submit that claim 1 particularly points out and distinctly claims the subject matter which Applicants regard as their invention. Withdrawal of this rejection is respectfully requested.

*Rejections Under 35 U.S.C. § 112, 1st Paragraph*

**Rejection of claims 17-20**

Claims 17-20 were rejected under 35 U.S.C. § 112, 1st paragraph because the specification allegedly does not provide enablement for a dyestuff, antibacterial, or herbicidal use. The Examiner stated "that the specification did not explicitly describe any dyestuff, antibacterial or herbicidal composition or use." Office Action at page 4. This rejection is respectfully traversed.

Clarification of this rejection is requested. The Examiner has not alleged that undue experimentation would be necessary to practice the invention, and he has not presented an analysis under *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The Examiner is reminded that absence of working examples will not by itself render an invention non-enabled. MPEP § 2164.02. Withdrawal of this rejection is respectfully requested.

**Rejection of claim 17**

Claim 17 was rejected under 35 U.S.C. § 112, 1st paragraph by virtue of recitation of *use of*, which the Examiner alleged is indefinite.

Applicants note that a rejection for indefiniteness is not properly made under 35 U.S.C. § 112, 1st paragraph. Nevertheless, Applicants have cancelled claim 17 and added new claim 22, drawn to a method of treating HIV or AIDS. Withdrawal of this aspect of the rejection is respectfully requested.

Claim 17 was also rejected because the Examiner alleged that the specification does not reasonably provide enablement for the treatment of HIV or AIDS. The Examiner has presented an analysis under *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and has concluded that undue

experimentation would be required "to test which disease can be treated by the compounds of the instant claims, with no assurance of success." Office Action at page 10. This rejection is respectfully traversed.

The Examiner's *Wands* analysis is flawed in several respects which include,

1. The Examiner apparently considers HIV infection to include a myriad of other viral infections. Thus at page 8, lines 1 and 2, he stated, "[t]here are insufficient exemplifications to support the treatment of all known viral infections encompassed by claim 17...," and at page 9, lines 4-6, he stated, "[o]ne skilled in the art would need to determine which HIV infections out of all such known infections would be benefited by the compounds of claim 1...." (emphasis added). In addition, at page 9, lines 1 and 2, the Examiner stated, "[t]he claims are drawn to the treatment of any and all for [sic] HIV or AIDS;" at page 7, lines 3-6, the Examiner stated, "in the absence of a showing of a nexus between any and all known viral infections and the claimed compounds, one of ordinary skill in the art is unable to fully predict possible results from the administration of the claimed compounds" (emphasis added); at page 9, lines 9-13, the Examiner stated, "each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine ... which viral infections would benefit from this activity;" and at page 9, lines 14-17, the Examiner stated, "the specification fails to provide sufficient support of the broad method recited in applicants' claims. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound in order the practice the claimed invention." (emphasis added).

The human immunodeficiency virus (HIV) is a virus that can cause AIDS. Either one is infected by HIV or one is not. If one is infected with the virus, one has a single infection; there is no plurality of HIV infections. Infection is confirmed by screening a person's blood for the presence of antibodies to HIV. The term AIDS applies to the most advanced stages of HIV infection. Opportunistic infections are common in people with AIDS. Such infections include conjunctivitis, ear infections, tonsillitis, and various cancers. Opportunistic infections may be caused by bacteria, viruses, yeast, fungi, and other microbes; AIDS patients are at risk for such infections because their immune system is compromised by HIV. Opportunistic infections are typically treated with separate drugs. In support of the above arguments, Applicants provide

herewith a copy of *HIV Infection and AIDS* from the WebMD website, which may assist the Examiner. Therefore, the Examiner's concerns *supra* regarding the number of viral infections encompassed by present claim 17 are incorrect and unjustified. Furthermore, Applicants are not claiming using all of the compounds prepared by the process of claim 1 to treat HIV/AIDS. Claim 17 recites only seven compounds.

2. The Examiner has required absolute predictability between *in vitro* activity and the treatment of viral conditions such as HIV (see above). Further, the Examiner stated that *in vitro* data are not "a reliable predictor of success even in view of the seemingly high level of skill in the art." Office Action at pages 5-6. (emphasis added). Absolute predictability is not the standard employed in the patent statutes. Reasonable correlation of *in vitro* data to therapeutic utility or reasonable predictability is the correct standard. MPEP § 2107.03. However, the Examiner has not documented his statement regarding *in vitro* data as a reliable predictor. See the following point.

3. The Examiner has set forth no basis for dismissing Applicants' results with acutely infected H9 cells. In fact, infected H9 cells are widely used to assay a potential anti-HIV therapeutic, and *in vivo* assays with therapeutics showing positive results *in vitro* are well-established in the art. Reduction of p24 antigen levels in H9 cells *in vitro* over levels observed for untreated controls indicates that the therapeutic is effective for treatment of HIV infection. See for example, Robert Gallo's US Patent 6,620,416 at columns 64-65. According to Dr. Gallo, the eminent scientist who co-discovered that HIV is the cause of AIDS, "[o]nce the therapeutic has been tested *in vitro*, and also preferably in a non-human model, the utility of the therapeutic can be determined by testing in human subjects." US Patent 6,620,416 at column 64, lines 62-64. (emphasis added). In other words, one could also proceed directly to human testing after a successful result in infected H9 cells. Dr Gallo then goes on to detail, at column 64, line 67 to column 65, line 21, the well-established *in vivo* tests that are currently in use.

4. As pointed out at page 5 of the WebMD article, AIDS treatment has progressed substantially in the last 10 years. Many classes of drugs are now available for treating HIV infection or AIDS. Accordingly, mere mention (Office Action ant page 5) that the nature of the invention is a method for the treatment of HIV or AIDS is not an indicium of undue experimentation.

Therefore, the HIV/AIDS art has advanced to a stage where one can reasonably predict based on *in vitro* tests whether a therapeutic agent will be effective in vivo. While some experimentation may be necessary, some experimentation is permissible. Applicants submit that the routineer would be able to use the knowledge in this art to determine if the claimed compounds were effective to treat HIV/AIDS in a mammal without undue experimentation. Therefore, submission of "proof that the claimed compounds or compositions have ever been administered to a human or to an animal model or [sic – other] than mice," as required by the Examiner at page 7, lines 7-9 and at page 8, last three lines is unnecessary.

Withdrawal of this aspect of the rejection is respectfully requested.

*Rejection Under 35 U.S.C. § 102(b)*

Claims 1-20 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kashiwada et al., *Tetrahedron* **2001**, *57*, 1559-1563. The Examiner directed attention to page 1560, right column, last paragraph and Scheme 1 and to page 1562, first paragraph. This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Moreover, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*,

17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Applicants' invention is *inter alia* a total synthesis of benzo[b]pyrenes from the condensation of a dihydroxybenzoic acid derivative with an $\alpha,\beta$-unsaturated aldehyde in the presence of effective amounts of specific reagents and microwave irradiation. Contrariwise, Kashiwada et al. does not disclose a total synthesis. Presumably, the Examiner has pointed to page 1560 for the disclosure of compounds 3 and 3'. However, compounds 3 and 3' of Kashiwada et al. were not synthesized at all; they were extracted and isolated from the leaves and twigs of *Rhododendron dauricum*. See Kashiwada et al., page 1559, first paragraph under *2. Results and discussion.* The passages cited by the Examiner do not disclose Applicants' condensation reaction to prepare compounds 3 and 3'. In Kashiwada et al., the compounds are merely extracted from the leaves and twigs of *Rhododendron dauricum*, isolated and purified, but not synthesized from smaller molecules. Therefore, because every element of Applicants' process claims is not identically disclosed in Kashiwada et al., there can be no anticipation of present claims 1-16.

The Examiner has also pointed to the first paragraph of page 1562, presumably as basis for rejection of claims 17-20. Since no basis for the rejection of these claims has been articulated, clarification is requested. Applicants note initially that the Examiner has employed the infamous *Biotech Squeeze*, which has long ago been held improper by the USPTO: the Examiner on one hand considers Applicants' specification non-enabled under § 112 first paragraph because of the alleged absence of established correlation between *in vitro* activity and the treatment of viral conditions such as HIV *in vivo*, and on the other hand considers the same *in vitro* activity (against acutely infected H9 cells) disclosed in Kashiwada et al. sufficient to render the document enabling for a 102(b) rejection of Applicants' method claim 17. Applicants respectfully submit that the Examiner cannot have it both ways. The solution to the *Biotech Squeeze* frequently enunciated publicly by USPTO representatives is that the Examiner must choose to make or maintain one or the other rejection, but not both.

Even if Kashiwada et al. is enabled, the passage at page 1562 does not disclose treatment of HIV infection or AIDS in a mammal, does not disclose a pharmaceutical composition, does not disclose a dyestuff, and does not disclose an antibacterial or herbicidal composition, as

required by present claims 17-20. Anti-HIV activity against acutely infected H9 cells is not identical to *in vivo* treatment in a mammal in need of such treatment. Therefore, because every element of Applicants' composition and method of use claims is not identically disclosed in Kashiwada et al., there can be no anticipation of present claims 17-20.

Withdrawal of this rejection is respectfully requested.

*Rejection Under 35 U.S.C. § 103(a)*

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kashiwada et al., *Tetrahedron* **2001**, *57*, 1559-1563. The Examiner stated that "Kashiwada et al. teach preparation of compounds of applicants' formula (1) and their use in the same type manner as recited in the claims." Office Action at page 11. The Examiner again directed attention to page 1560, right column, last paragraph and Scheme 1 and to page 1562, first paragraph.

Furthermore, the Examiner stated that Kashiwada et al. differs from the claimed invention by virtue of the fact that Kashiwada et al. does not explicitly teach the use of microwave radiation; rather Kashiwada et al. does teach irradiating with a low-pressure mercury lamp, which, the Examiner argued, inherently contains microwave irradiation. *Ibid.* Therefore, the Examiner concluded it would have been obvious to one of ordinary skill in the art to apply the inherent teachings of Kashiwada et al. in the production of the claimed product. Office Action at page 12. Finally, the Examiner stated that claim 19 was rejected because "the claimed compounds have color characteristics and would inherently have utility as a dyestuff." *Ibid.*

This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

The Examiner is incorrect that Kashiwada et al. *prepares* compounds falling within Applicants' generic formula I, and he is incorrect that the only difference between Kashiwada et al. and the present claims is the use of microwave irradiation. As pointed out *supra*, applicants' invention is *inter alia* a total synthesis of benzo[b]pyrenes from the condensation of a dihydroxybenzoic acid derivative with an $\alpha,\beta$-unsaturated aldehyde in the presence of effective amounts of specific reagents and microwave irradiation. Contrariwise, Kashiwada et al. does not disclose a total synthesis. Presumably, the Examiner has pointed to page 1560 for the disclosure of compounds 1, 2, 3 and 3'. However, these compounds of Kashiwada et al. were not synthesized at all; they were extracted and isolated from the leaves and twigs of *Rhododendron dauricum*. See Kashiwada et al., page 1559, first paragraph under *2. Results and discussion.* The passages cited by the Examiner do not disclose Applicants' condensation reaction to prepare compounds 1, 2, 3 and 3'. In Kashiwada et al., the compounds are merely extracted from the leaves and twigs of *Rhododendron dauricum*, isolated and purified, but not synthesized from smaller molecules.

Furthermore, Kashiwada et al. employs a low-pressure mercury lamp to cyclize compounds 3 and 3' and thereby to form compounds 1 and 2, so as to confirm the structures of compounds 1 and 2. Therefore, Kashiwada et al. is not using a low-pressure mercury lamp to prepare compounds 3 and 3' via the condensation of a dihydroxybenzoic acid derivative with an $\alpha,\beta$-unsaturated aldehyde in the presence of effective amounts of specific reagents, as presently claimed. Nor is Kashiwada et al. cyclizing compounds 3 and 3' after their preparation via the condensation of a dihydroxybenzoic acid derivative with an $\alpha,\beta$-unsaturated aldehyde in the presence of effective amounts of specific reagents and irradiation, as presently claimed.

Therefore, because modification of Kashiwada et al. as proposed by the Examiner would not result in Applicants' invention, Kashiwada et al. lacks all the elements of Applicants' claims. As such, there is no *prima facie* case of obviousness. Similarly, there is no motivation or reasonable expectation of success in Kashiwada et al. to synthesize the compounds disclosed therein from smaller molecules, as opposed to extracting and isolating them from a natural source. Because such motivation and reasonable expectation of success can come only from Applicants' specification, there is no *prima facie* case of obviousness.

The Examiner has not articulated how claims 17-20 differ from Kashiwada et al. The

difference set forth by the Examiner at page 11 of the Office Action (absence of microwave irradiation from Kashiwada et al.) applies only to the method of making claims. Clarification is requested. Applicants do not understand the Examiner's allegation that the claimed compounds have color characteristics. Kashiwada et al. discloses that rhododaurichromanic acid A (compound 1) is a white powder, rhododaurichromanic acid B (compound 2) is a white powder, and daurichromanic acid (compound 3) is a colorless syrup. Clarification is again requested.

Withdrawal of this rejection is respectfully requested.

## CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (703) 239-9592 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

ZHENDONG JIN ET AL.

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 19 day of May, 2005.

CANDIS BRENDING
Name

_____
Signature

# HIV Infection and AIDS

*By The National Institute of Allergy and Infectious Diseases*
*WebMD Public Information from the National Institutes of Health*

AIDS — acquired immune deficiency syndrome — was first reported in the United States in 1981 and has since become a major worldwide epidemic. AIDS is caused by the human immunodeficiency virus (HIV). By killing or impairing cells of the immune system, HIV progressively destroys the body's ability to fight infections and certain cancers. Individuals diagnosed with AIDS are susceptible to life-threatening diseases called opportunistic infections, which are caused by microbes that usually do not cause illness in healthy people.

More than 600,000 cases of AIDS have been reported in the United States since 1981, and as many as 900,000 Americans may be infected with HIV. The epidemic is growing most rapidly among minority populations and is a leading killer of African-American males. According to the U.S. Centers for Disease Control and Prevention (CDC), the prevalence of AIDS is six times higher in African-Americans and three times higher among Hispanics than among whites.

## Transmission

HIV is spread most commonly by sexual contact with an infected partner. The virus can enter the body through the lining of the vagina, vulva, penis, rectum or mouth during sex.

HIV also is spread through contact with infected blood. Prior to the screening of blood for evidence of HIV infection and before the introduction in 1985 of heat-treating techniques to destroy HIV in blood products, HIV was transmitted through transfusions of contaminated blood or blood components. Today, because of blood screening and heat treatment, the risk of acquiring HIV from such transfusions is extremely small.

HIV frequently is spread among injection drug users by the sharing of needles or syringes contaminated with minute quantities of blood of someone infected with the virus. However, transmission from patient to health-care worker or vice-versa via accidental sticks with contaminated needles or other medical instruments is rare.

Women can transmit HIV to their fetuses during pregnancy or birth. Approximately one-quarter to one-third of all untreated pregnant women infected with HIV will pass the infection to their babies. HIV also can be spread to babies through the breast milk of mothers infected with the virus. If the drug AZT is taken during pregnancy, the chance of transmitting HIV to the baby is reduced significantly. If AZT treatment of mothers is combined with cesarean sectioning to deliver infants, infection rates can be reduced to 1 percent.

Although researchers have detected HIV in the saliva of infected individuals, no evidence exists that the virus is spread by contact with saliva. Laboratory studies reveal that saliva has natural compounds that inhibit the infectiousness of HIV. Studies of people infected with HIV have found no evidence that the virus is spread to others through saliva such as by kissing. No one knows, however, the risk of infection from so-called "deep" kissing, involving the exchange of large amounts of saliva, or by oral intercourse. Scientists also have found no evidence that HIV is spread through sweat, tears, urine or feces.

Studies of families of HIV-infected people have shown clearly that HIV is not spread through casual contact such as the sharing of food utensils, towels and bedding, swimming pools, telephones or toilet seats. HIV is not spread by biting insects such as mosquitoes or bedbugs.

HIV can infect anyone who practices risky behaviors such as:

- sharing drug needles or syringes;
- having sexual contact without using a latex male condom with an infected person or with someone whose HIV status is unknown.

Having another sexually transmitted disease such as syphilis, herpes, chlamydial infection, gonorrhea or bacterial vaginosis appears to make someone more susceptible to acquiring HIV infection during sex with an infected partner.

**Early Symptoms**

Many people do not develop any symptoms when they first become infected with HIV. Some people, however, have a flu-like illness within a month or two after exposure to the virus. They may have fever, headache, malaise and enlarged lymph nodes (organs of the immune system easily felt in the neck and groin). These symptoms usually disappear within a week to a month and are often mistaken for those of another viral infection. People are very infectious during this period, and HIV is present in large quantities in genital secretions.

More persistent or severe symptoms may not surface for a decade or more after HIV first enters the body in adults, or within two years in children born with HIV infection. This period of "asymptomatic" infection is highly variable. Some people may begin to have symptoms in as soon as a few months, whereas others may be symptom-free for more than 10 years. During the asymptomatic period, however, HIV is actively

multiplying, infecting and killing cells of the immune system. HIV's effect is seen most obviously in a decline in the blood levels of CD4+ T cells (also called T4 cells) -- the immune system's key infection fighters. The virus initially disables or destroys these cells without causing symptoms.

As the immune system deteriorates, a variety of complications begins to surface. One of the first such symptoms experienced by many people infected with HIV is large lymph nodes or "swollen glands" that may be enlarged for more than three months. Other symptoms often experienced months to years before the onset of AIDS include a lack of energy, weight loss, frequent fevers and sweats, persistent or frequent yeast infections (oral or vaginal), persistent skin rashes or flaky skin, pelvic inflammatory disease that does not respond to treatment, or short-term memory loss.

Some people develop frequent and severe herpes infections that cause mouth, genital or anal sores, or a painful nerve disease known as shingles. Children may have delayed development or failure to thrive.

**AIDS**

The term AIDS applies to the most advanced stages of HIV infection. Official criteria for the definition of AIDS are developed by the CDC in Atlanta, GA, which is responsible for tracking the spread of AIDS in the United States.

In 1993, CDC revised its definition of AIDS to include all HIV-infected people who have fewer than 200 CD4+ T cells. (Healthy adults usually have CD4+ T-cell counts of 1,000 or more.) In addition, the definition includes 26 clinical conditions that affect people with advanced HIV disease. Most AIDS-defining conditions are opportunistic infections, which rarely cause harm in healthy individuals. In people with AIDS, however, these infections are often severe and sometimes fatal because the immune system is so ravaged by HIV that the body cannot fight off certain bacteria, viruses and other microbes.

Opportunistic infections common in people with AIDS cause such symptoms as coughing, shortness of breath, seizures, mental symptoms such as confusion and forgetfulness, severe and persistent diarrhea, fever, vision loss, severe headaches, weight loss, extreme fatigue, nausea, vomiting, lack of coordination, coma, abdominal cramps, or difficult or painful swallowing.

Although children with AIDS are susceptible to the same opportunistic infections as adults with the disease, they also experience severe forms of the bacterial infections to which children are especially prone, such as conjunctivitis (pink eye), ear infections and tonsillitis.

People with AIDS are particularly prone to developing various cancers, especially those caused by viruses such as Kaposi's sarcoma and cervical cancer, or cancers of the immune system known as lymphomas. These cancers are usually more aggressive and difficult to treat in people with AIDS. Hallmarks of Kaposi's sarcoma in light-skinned people are round brown, reddish or purple spots that develop in the skin or in the mouth. In dark-skinned people, the spots are more pigmented.

During the course of HIV infection, most people experience a gradual decline in the number of CD4+ T cells, although some individuals may

have abrupt and dramatic drops in their CD4+ T-cell counts. A person with CD4+ T cells above 200 may experience some of the early symptoms of HIV disease. Others may have no symptoms even though their CD4+ T-cell count is below 200.

Many people are so debilitated by the symptoms of AIDS that they are unable to hold steady employment or do household chores. Other people with AIDS may experience phases of intense life-threatening illness followed by phases of normal functioning.

A small number of people (less than 50) initially infected with HIV 10 or more years ago have not developed symptoms of AIDS. Scientists are trying to determine what factors may account for their lack of progression to AIDS, such as particular characteristics of their immune systems, or whether they were infected with a less aggressive strain of the virus or if their genetic make-up may protect them from the effects of HIV. Scientists hope that understanding the body's natural method of control may lead to ideas for protective HIV vaccines and use of vaccines to prevent disease progression.

**Diagnosis**

Because early HIV infection often causes no symptoms, it is primarily detected by testing a person's blood for the presence of antibodies (disease-fighting proteins) to HIV. HIV antibodies generally do not reach detectable levels until one to three months following infection and may take as long as six months to be generated in quantities large enough to show up in standard blood tests. HIV testing may also be performed on saliva and urine samples, in addition to blood samples.

People exposed to HIV should be tested for HIV infection as soon as they are likely to develop antibodies to the virus. Such early testing will enable them to receive appropriate treatment at a time when they are most able to combat HIV and prevent the emergence of certain opportunistic infections (see "Treatment" below). Early testing also alerts HIV-infected people to avoid high-risk behaviors that could spread HIV to others.

HIV testing is done in most doctors' offices or health clinics and should be accompanied by counseling. Individuals can be tested anonymously at many sites if they have particular concerns about confidentiality. In addition, blood samples for anonymous HIV testing may now be collected at home. Home-based test kits are available by telephone order or over the counter at pharmacies.

Two different types of antibody tests, ELISA and Western Blot, are used to diagnose HIV infection. If a person is highly likely to be infected with HIV and yet both tests are negative, a doctor may test for the presence of HIV itself in the blood. The person also may be told to repeat antibody testing at a later date, when antibodies to HIV are more likely to have developed.

Babies born to mothers infected with HIV may or may not be infected with the virus, but all carry their mothers' antibodies to HIV for several months. If these babies lack symptoms, a definitive diagnosis of HIV infection using standard antibody tests cannot be made until after 15 months of age. By then, babies are unlikely to still carry their mothers' antibodies and will have produced their own, if they are infected. New technologies

to detect HIV itself are being used to more accurately determine HIV infection in infants between ages 3 months and 15 months. A number of blood tests are being evaluated to determine if they can diagnose HIV infection in babies younger than 3 months.

**Treatment**

When AIDS first surfaced in the United States, no drugs were available to combat the underlying immune deficiency and few treatments existed for the opportunistic diseases that resulted. Over the past 10 years, however, therapies have been developed to fight both HIV infection and its associated infections and cancers.

The Food and Drug Administration has approved a number of drugs for the treatment of HIV infection. The first group of drugs used to treat HIV infection, called nucleoside analog reverse transcriptase inhibitors (NRTIs), interrupt an early stage of virus replication. Included in this class of drugs are zidovudine (also known as AZT), zalcitabine (ddC), didanosine (ddI), stavudine (D4T), lamivudine (3TC) and abacavir succinate. These drugs may slow the spread of HIV in the body and delay the onset of opportunistic infections. Importantly, they do not prevent transmission of HIV to other individuals. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as delavirdine, nevirapine and efavirenz are also available for use in combination with other antiretroviral drugs.

A third class of anti-HIV drugs, called protease inhibitors, interrupts virus replication at a later step in its life cycle. They include ritonavir, saquinivir, indinavir and nelfinavir. Because HIV can become resistant to each class of drugs, combination treatment using both is necessary to effectively suppress the virus.

Currently available antiretroviral drugs do not cure people of HIV infection or AIDS, however, and they all have side effects that can be severe. AZT may cause a depletion of red or white blood cells, especially when taken in the later stages of the disease. If the loss of blood cells is severe, treatment with AZT must be stopped. Ddl can cause an inflammation of the pancreas and painful nerve damage.

The most common side effects associated with protease inhibitors include nausea, diarrhea and other gastrointestinal symptoms. In addition, protease inhibitors can interact with other drugs resulting in serious side effects. Investigators also recently have reported cases of abnormal redistribution of body fat among some individuals receiving protease inhibitors.

A number of drugs are available to help treat opportunistic infections to which people with HIV are especially prone. These drugs include foscarnet and ganciclovir, used to treat cytomegalovirus eye infections, fluconazole to treat yeast and other fungal infections, and TMP/SMX or pentamidine to treat *Pneumocystis carinii* pneumonia (PCP).

In addition to antiretroviral therapy, adults with HIV whose CD4+ T-cell counts drop below 200 are given treatment to prevent the occurrence of PCP, which is one of the most common and deadly opportunistic infections associated with HIV. Children are given PCP preventive therapy when their CD4+ T-cell counts drop to levels considered below normal for their age group. Regardless of their CD4+ T-cell counts, HIV-infected children and adults who have survived an episode of PCP are

given drugs for the rest of their lives to prevent a recurrence of the pneumonia.

HIV-infected individuals who develop Kaposi's sarcoma or other cancers are treated with radiation, chemotherapy or injections of alpha interferon, a genetically engineered naturally occurring protein.

**Prevention**

Since no vaccine for HIV is available, the only way to prevent infection by the virus is to avoid behaviors that put a person at risk of infection, such as sharing needles and having unprotected sex.

Because many people infected with HIV have no symptoms, there is no way of knowing with certainty whether a sexual partner is infected unless he or she has been repeatedly tested for the virus or has not engaged in any risky behavior. CDC recommends that people either abstain from sex or protect themselves by using male latex condoms whenever having oral, anal or vaginal sex. Only male condoms made of latex should be used, and water-based lubricants should be used with latex condoms.

Although some laboratory evidence shows that spermicides can kill HIV organisms, in clinical trials, researchers have not found that these products can prevent HIV.

The risk of HIV transmission from a pregnant woman to her fetus is significantly reduced if she takes AZT during pregnancy, labor and delivery, and her baby takes it for the first six weeks of life.

**Research**

NIAID-supported investigators are conducting an abundance of research on HIV infection, including the development and testing of HIV vaccines and new therapies for the disease and some of its associated conditions. More than a dozen HIV vaccines are being tested in people, and many drugs for HIV infection or AIDS-associated opportunistic infections are either in development or being tested. Researchers also are investigating exactly how HIV damages the immune system. This research is suggesting new and more effective targets for drugs and vaccines. NIAID-supported investigators also continue to document how the disease progresses in different people.

For information about studies of new HIV therapies, call the AIDS Clinical Trials Information Service:

1-800-TRIALS-A
1-800-243-7012 (TDD/Deaf Access)

For federally approved treatment guidelines on HIV/AIDS, call the HIV/AIDS Treatment Information Service:

1-800-HIV-0440
1-800-243-7012 (TDD/Deaf Access)

NIAID, a component of the National Institutes of Health (NIH), supports research on AIDS, tuberculosis, malaria and other infectious diseases, as well as allergies and immunology. NIH is an agency of the U.S.

Department of Health and Human Services.

"The National Institute of Allergy and Infectious Diseases. HIV Infection and AIDS. March 1999. (Online) http://www.niaid.nih.gov/factsheets/hivinf.htm"